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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/602,272	02/16/96	ELLIOTT M	KIR96-01

EXAMINER	
CANELLA, K	
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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
08/602,272	Elliott et al
Examiner	**Art Unit**
Karen Canella	1642

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3 months* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☐ Responsive to communication(s) filed on _____

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *6-10, 12-32, and 34-50* is/are pending in the applica

4a) Of the above, claim(s) *16-28 and 38-50* is/are withdrawn from considera

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *6-10, 12-15, 29-32, and 34-37* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirem

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
18) ☐ Interview Summary (PTO-413) Paper No(s). _____
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other:

DETAILED ACTION

1. The request filed on August 10, 2001 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 08/602,272 is acceptable and a CPA has been established. An action on the CPA follows.

2. Claims 6, 8-10, 12-15, 29-32 and 34-37 have been amended. Claims 6-10, 12-32 and 34-50 are pending. Claims 16-28 and 38-50 remain withdrawn from consideration. Claims 6, 8-10, 12-15, 29-32 and 34-37 are examined on the merits.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 15 and 37 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Independent claims 14 and 36 recite: "wherein the chimeric antibody competitively inhibits the binding of TNF-alpha to monoclonal antibody cA2". This statement is not unclear, however, dependent claims 15 and 37 recite: "wherein the chimeric antibody is the monoclonal antibody cA2" and it is unclear how a single monoclonal antibody can compete with itself for binding to a protein. For purpose of examination, claims 15 and 37 will be read as depending on claims 13 and 35, respectively.

Claim Rejections - 35 USC § 102

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

6. Claims 6, 8, 10, 12-15, 29, 30, 32 and 34-37 are rejected under 35 U.S.C. 102(a) as being anticipated by Hommes et al (Gastroenterology, 1995, Vol. 108, No. 4, suppl., p. A838, as evidenced by Leardi et al (Italian Journal of Surgical Sciences, 1983, Vol. 13, pp. 197-201) and Le et al (US 5,919,492). Claim 6 is drawn to a method of treating or preventing thrombosis in a subject suffering from or at risk of thrombosis comprising administering a therapeutically effective amount of a tumor necrosis factor antagonist to the subject. Claim 29 is drawn to a method of decreasing plasma fibrinogen in a subject suffering from or at risk of thrombosis comprising administering a therapeutically effective amount of a tumor necrosis factor antagonist to the subject. Claims 8 and 30 encompass the antagonist as an anti-tumor necrosis factor antibody or an antigen-binding fragment thereof. Claims 10, 13, 32 and 35 specify the binding of the antibody to the epitopes consisting of amino acids 87-108 and 59-80 of human tumor necrosis factor. Claims 12 and 34 encompass a chimeric antibody comprising a non-human variable region specific for TNF and a human constant region. Claims 14 and 36 specify that the chimeric antibody inhibits the binding of TNF-alpha to the monoclonal antibody cA2. Claims 15 and 37 specify that the chimeric monoclonal antibody is cA2. Hommes et al disclose that treatment of patients with Crohn's disease with the chimeric antibody cA2 decreases thrombocytosis and hyperfibrinogenemia in said patients. Leardi et al disclose that patients with Crohn's disease are at risk and/or suffering from thrombosis as a result of thrombocytosis and hyperfibrinogenemia. Le et al discloses that the chimeric monoclonal antibody cA2 recognizes two peptide sequences of TNF-alpha consisting of the fragments defined by amino acids 87-108, and amino acids ~~87-108~~ 59-80. Thus, the method of treatment disclosed by Hommes et al, comprising the administration of the antibody cA2, meets all the embodiments of claims 6, 8, 10, 12-13, 15, 29, 30, 32, 34, 35 and 37. Further, Le et al discloses antibodies which compete with cA2 for binding to TNF-alpha (column 11, lines 39-50) and methods for obtaining said antibodies (column 17, lines 57-67), thus disclosing the embodiments of claims 14 and 36.

7. Claims 6 and 8 are rejected under 35 U.S.C. 102(b) as being anticipated by either of Arii et al (Circulation, 1994, Vol. 90, No. 4, part 2, p. I522, abstract No. 2811) or Vertrees et al

(Asaio Journal, 1994, Vol. 40, pp. M554-M559) or Wakefield et al (Arteriosclerosis, Thrombosis and Vascular Biology, 1995, Vol. 15, pp. 258-268).. Claims 6 is draw to a method of treating or preventing thrombosis comprising administering a therapeutically effective amount of tumor necrosis factor antagonist. Claim 8 embodies the antagonist as an anti-tumor necrosis factor antibody or an antigen-binding fragment thereof.

Arii et al disclose a method of treating rats suffering from acute myocardial infarction comprising the administration of an anti-tumor necrosis factor antibody. As it is well known in the art that subjects suffering from myocardial infarction are at risk for a secondary thrombus, the method disclosed by Arii et al is a method of preventing thrombosis.

Vertrees et al disclose a method for preventing coagulopathy in pigs undergoing cardiopulmonary bypass comprising the administration of a TNF-murine monoclonal antibody. Vertrees et al disclose that TNF is the agent responsible for post-operative coagulopathy.

Wakefield et al disclose a method of treating rats suffering from venous thrombosis comprising the administration of neutralizing antibodies to TNF, thus the disclosure of Wakefiled et al comprises a method of treating thrombosis.

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was

made in order for the examiner to consider the applicability of 35 U.S.C. 103© and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

10. Claims 6, 8, 9, 29, 30 and 31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hommes et al (Gastroenterology, 1995, Vol. 108, No. 4, suppl., p. A838, as evidenced by Leardi et al (Italian Journal of Surgical Sciences, 1983, Vol. 13, pp. 197-201) and Le et al (US 5,919,492) in view of Dhainaut et al (Critical Care Medicine, 1995, Vol. 23, pp. 1461-1469). The embodiments of claims 6, 8, 29 and 30 are stated in paragraph 6, supra. Claims 9 and 31 further embody a humanized or resurfaced antibody or an antigen-binding fragment thereof. Hommes et al teach a method of treating or preventing thrombosis, and a method of decreasing plasma fibrinogen comprising the administration of a chimeric anti-TNF monoclonal antibody, having a non-human variable region and a human constant region. Hommes et al do not teach the administration of a humanized anti-TNF monoclonal antibody. Dhainaut et al teach a method of treating patients suffering from septic shock comprising the administration of a humanized anti-TNF-alpha antibody, CDP571. It would have been *prima facia* obvious to one of ordinary skill in the art at the time the claimed invention was made to administer the CDP571 humanized antibody for the treatment or prevention of thrombosis and the reduction of plasma fibrinogen. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of Dhainaut et al on the ability of the humanized CDP571 to induce a dose dependent reduction in circulating TNF levels in patients suffering from sepsis as well as to be well tolerated in said patients.

11. Claims 6 and 8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fisher et al (Critical Care Medicine, 1993, Vol. 21, pp. 318-327) in view of Hopper et al (Blood, 1994, Vol. 84, pp. 483-489) or Jolin et al (Acta Anaesthesiologica Scandinavica, Supplementum, 1991, Vol. 95, pp. 40-52). Claims 6 is draw to a method of treating or preventing thrombosis comprising administering a therapeutically effective amount of tumor necrosis factor antagonist. Claim 8 embodies the antagonist as an anti-tumor necrosis factor antibody or an antigen-binding fragment

thereof. Fischer et al teach a method of treating sepsis in patients presenting with elevated levels of TNF, comprising the administration of an anti-TNF monoclonal antibody. Fischer et al do not teach a method for treating or preventing thrombosis comprising the administration of said monoclonal antibody. Hooper et al teach that patients with AIDS are at risk for thrombosis due to the presence of TNF-alpha. Jolin et al teach that patients with Adult Respiratory Distress Syndrome(ARMS) have elevated procoagulation factors induced by TNF, and thus said patients are at risk of thrombosis. Jolin et al suggest that antibodies against TNF should be used in future ARMS therapy. It would have been *prima facia* obvious to one of ordinary skill in the art at the time the claimed invention was made to administer an anti-tumor necrosis factor antibody to patients suffering from ,or at risk of, thrombosis. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of Fischer et al on the efficacy of administering an anti-tumor necrosis factor antibody to a patient presenting with high level of TNF, and the teachings of Hopper et al and Jolin et al on patients suffering from or at risk of thrombosis mediated by elevated levels of TNF.

12. Claims 6, 8, 10, 12-15, 29, 30, 32 and 34-37 rejected under 35 U.S.C. 103(a) as being unpatentable over Le et al (US 5,656,272) in view of Hopper et al (Blood, 1994, Vol. 84, pp. 483-489) or Jolin et al (Acta Anaesthesiologica Scandinavica, Supplementum, 1991, Vol. 95, pp. 40-52). The embodiments of the claims are stated in paragraph 6, supra. Le et al teach a method of treating Chron's disease by the administration of the chimeric cA2 antibody, which binds to epitopes defined by amino acids 87-108 and 59-80 of human TNF. Le et al further contemplates monoclonal antibodies which compete with cA2 for binding to TNF and methods for obtaining said antibodies. Le et al teach that these antibodies have the ability to neutralize TNF activity and thus ameliorate the pathology of Crohn's disease. Le et al do not teach the administration of cA2 or antibody which competes with cA2 for binding to TNF, as a method of treating thrombosis. Hooper et al teach that patients with AIDS are at risk for thrombosis due to the presence of TNF-alpha. Jolin et al teach that patients with Adult Respiratory Distress Syndrome(ARMS) have elevated procoagulation factors induced by TNF, and thus said patients are at risk of thrombosis.

Jolin et al suggest that antibodies against TNF should be used in future ARMS therapy. It would have been *prima facia* obvious to one of ordinary skill in the art at the time the claimed invention was made to administer cA2, or antibodies which compete with cA2 for binding to TNF, to patients suffering from, or at risk of, thrombosis. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of Fischer et al on the efficacy of administering an anti-tumor necrosis factor antibody to a patient presenting with high level of TNF, and the teachings of Hopper et al and Jolin et al on patients suffering from or at risk of thrombosis mediated by elevated levels of TNF.

Conclusion

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen Canella whose telephone number is (703) 308-8362. The examiner can normally be reached on Monday through Friday from 8:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (703) 308-3995. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

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Patent Examiner, Group 1642
September 17, 2001

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